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The following details have been taken from the documents submitted by the Applicant

54 Magazine for storing test elements

57 The subject-matter of the invention is a magazine for storing test elements with one or more test zones which are attached next to one another on a rectangular carrier, the magazine having at least one pair of opposite guide grooves, into which the test elements are pushed in such a way that they lie directly next to one another and edges of neighbouring carriers butt against one another.

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TRANSLATION FROM GERMAN

Description

The present invention lies in the area of storing test elements, as are used for the detection of analytes in test fluids. Such test elements are used especially in the area of urine analysis and in the area of blood sugar determination. Furthermore, test elements are used extensively in environmental analytics. A further area of increasing significance concerns immunological tests, for example the detection of drugs, HCG and HIV in blood or urine.

For carrying out the detection of an analyte or the analysis of a test fluid, the test element is brought into contact with a sample. This may involve, for example, rubbing down a surface with the test element. However, the normal field of application of test elements lies in the analysis of test fluids, for which the test fluid is either applied to the test element (especially determinations from blood, serum, liquor) or the test elements is dipped into the test fluid (especially urine).

The majority of test elements must be protected against moisture in order to avoid decomposition of reagents. This applies as much to the so-called optical test strips, in which a colour change is induced by reaction of an analyte with the sample, as it does to so-called sensor elements, in which a chemical change of the test elements induced by the sample is evaluated electrochemically. Furthermore, it is normally necessary to protect test elements from mechanical influences and soiling to ensure reliable analysis results. In the prior art, several ways of storing test elements are known. In the first procedure, the test elements are loose in a vessel, for example a tube, which can be closed by a stopper or the like. Furthermore, it is known to seal test elements individually in water-vapour-impermeable films. With the storing methods mentioned, it is difficult however for the test elements to be mechanically taken out of the storage vessel or sealing film. In connection with a mechanical removal of test elements, the prior art discloses a series of magazines, as are described for example in the patents US-5,102,624, US-5,154,889, US-3,918,910, US-4,911,344 and US-4,142,863. With this type of magazine, test elements which are stacked one on top of the other are used. The test elements described in these US patents are

specifically adapted for use in a magazine, i.e. they have a uniform thickness and can be displaced with respect to one another without catching or jamming. However, the majority of commercially available test elements do not have a uniform height profile and therefore cannot be readily used in the magazines of the prior art. In US Patent Specification 3,918,910 there is a description of a magazine which is suitable for storing test elements in which a plurality of detection zones have been applied to a carrier. For production reasons, the detection zones protrude above the carrier and thus cause a varying height structure of the test element. In Figures 5, 6, 7, 9 and 22 of US 3.918,910 there is shown a magazine which is suitable for storing test elements of this type. In the case of this magazine, the test elements are stacked one on top of the other, so that the upper side and underside of successive test elements respectively come to lie against one another. The stack of test elements is pressed by spring elements in the direction of an area from where the removal of a test element takes place by pushing out or pulling out. Experimental investigations have shown that magazines of this type are very prone to faults. Failures in which none of the test elements can be reliably gripped by the removal unit or two test elements are incorrectly transported together out of the magazine frequently occur.

The object of the present invention was to provide a magazine which operates reliably with the commercially popular test elements with a non-uniform height profile. Furthermore, it was the object of the present invention to provide a magazine with which mechanical removal is possible and which achieves a high packing density of the test elements.

It was found within the scope of the present invention that the problems occurring with a magazine according to US-3.918,910 are caused mainly by a tipping of the test elements. With reference to Figure 5 of US-3,918,910 (see Figure 6 of this application), this means that the test elements get into an inclined position with respect to the plate 61 or even that the plate 61 itself gets into an inclined position. This problem was observed in particular when the various test zones of an individual test element differ in their height, which is frequently the case with the commercially available test elements with a plurality of detection zones. It was further found that the flexible nature of the test elements allows a bending or even twisting of the test elements, so that reliable gripping of a test element of this type with a mechanical apparatus is difficult. The present invention therefore proposes a magazine in which the test elements are guided in guide grooves and are arranged in such a way that edges of neighbouring test elements come to lie directly against one another. The present invention uses the fact that, as a result of the way in which they are produced, the test elements have a width that is exactly defined and remains constant over the length of the test strip. If, as provided according to the invention, the test elements are guided with their two ends in grooves and the test elements are arranged next to one another instead of one above the other, as in the prior art, the test elements, or at least the two ends of the test elements, can

generally be positioned in a defined manner. Accordingly, reliable mechanical removal of test elements from the magazine can be realized with the present invention. In particular, the magazine of the present invention is suitable for the storing of test elements which are flexible and/or have a non-uniform height profile.

In Figures 1A and 1B of the present application, commercially available test elements are represented. Figure 1A shows a test element in plan view. The test element 1 has a carrier 2, to which a plurality of test zones 3 have been applied. The rectangular test element represented has a shorter side, which is referred to hereafter as the width, and a longer side, which is referred to as the length. In Figure 1B, a side view of a test element is represented. The different height of the test zones 3 and a bending of the test element can be clearly seen. The bending of the test element may be caused both by the properties of the carrier 2 and by the way in which the test zones 3 are applied. In a particularly favourable way of producing test elements, the test zones are applied to the carrier and subsequently covered with a fine netting. This procedure is described for example in US-3,802,842. The tendency to contract that is inherent in the netting causes a bending of the test element to take place. Furthermore, a bending may be induced by the carrier material. Plastic films which are cut into narrow strips during the production of the test elements are preferably used as carrier materials. A curving of the film caused by production can therefore also lead to a curving of the test element.

A magazine according to the invention for the storing of test elements has at least one pair of opposite guide grooves, into which the test elements to be stored are pushed. The guide grooves guide a test element respectively at the two of opposite ends. If a plurality of test elements are pushed one after the other into a guide groove, the test elements come to lie side-by-side and the longitudinal elements of the carriers of neighbouring test elements touch one another. The spacing of the opposite guide grooves is chosen to correspond to the length of the test elements. The spacing of the groove bases (regions of the grooves lying farthest apart) preferably corresponds to the length of a stretched-out test element. The depth of the grooves and the spacing of the grooves determine the length of the test element portion that is guided by the groove. If the spacing of the grooves at their lowest point corresponds to the length of the test elements, the guided length of the test elements is equal to the depth of the grooves. If, however, the grooves are further apart, the test elements have an amount of play in the longitudinal direction and the guided length corresponds to the depth of the grooves less this play. For the the magazine to work satisfactorily, a slight amount of play of the test elements in the longitudinal direction has proven to the favourable. This play is advantageously 0.5 to 20% of the length of the test elements. It has been found that it is generally adequate to guide the test elements over a length of 0.3 cm. The portions of the test strips that are guided by the grooves are preferably 0.4 to 1.0 cm long. According to the invention, embodiments in which the two grooves are in each case so deep that they receive

half of the test strip and the grooves continue to be connected to one another in such a way that a contiguous slit is obtained are also to be covered according to the invention. Within the scope of this invention, a slit of this type is understood as a special configuration of a pair of grooves. A slit of this type is favourable for the guiding of the test elements, since it can be used for suppressing the curving of the test elements, since the test elements are guided over the full length. However, magazine configurations in which the grooves have a depth of less than 2 cm are more advantageous in production engineering terms.

The length of the grooves determines the number of the test elements that can be received. There are scarcely any constraints on the length of the grooves. However, groove lengths of between 5 and 15 cm are favourable, since they lead to magazines which are compact and easy to handle. When using slits (instead of grooves) for receiving the test elements, their length is essentially limited by the technical constraints of moulds, since it is difficult to provide shaping moulds for great slit lengths, for example above 10 cm. This difficulty does not arise, however, when using grooves, and there are scarcely any limits on the length of the grooves. In both cases, i.e. both when using grooves and when using slits, it must be ensured that the grooves or the ends of the slits run essentially parallel, in order to avoid jamming or falling out of test elements.

According to the invention, it is advantageous if the magazine has pairs of guide grooves arranged one above the other, since the storage of test elements in layers arranged one above the other is possible, increasing the receiving capacity of the magazine. With regard to handling, it has proven to be favourable if a magazine has 8 to 15 layers of test elements. For example, for the storing of 300 test elements it is favourable to use a magazine with 12 layers, there being 25 test elements in each layer.

It was already mentioned at the beginning that, in addition to keeping the test elements in an orderly, readily available manner, the magazine can perform the task of protecting the test elements from moisture and mechanical effects. The magazine may therefore have walls which close off the inner space from the outer space. For the removal of test elements, the magazine must have one or more openings. These openings may be closed by a mechanical closure, for example a hinged lid or an adhesively attached sealing film. Furthermore, it is advantageous to seal the entire magazine, even when it is closed, in a water-vapour-impermeable outer packaging for transport.

In a preferred embodiment of the magazine, the guide grooves are integrated into the side walls of the magazine. Furthermore, the side walls may be connected to one another already during the production process by further walls, especially an upper wall and a lower wall. Arrangements of this type can preferably be produced integrally. In particular, the injection-moulding process is suitable for this. In technical mould-related terms, it may be more favourable, however, to form the walls of the magazine individually (advantageously by the injection-moulding process). Since the grooves of one side of the magazine are

formed by one mould half, the individual grooves have only small tolerances with respect to one another. If the parts of the magazine are formed individually, the side walls, upper side and lower side, front side and rear side are advantageously identical, so that the same moulds can be respectively used.

It is also advantageous, however, to form the walls individually in an injection-moulding process in such a way that they are connected to one another by film hinges. Such a formation (folding box) can be transformed into a magazine after demoulding by clipping together the individual walls.

In a further embodiment, the cassette is fitted together from n+1 injection-moulded parts, n being the number of layers of strips. All the parts are identical (repeat parts). They are flat frames which can be demoulded in an injection-moulding process without slides. If these frames are fitted flatly together (clipped, ultrasonically welded or adhesively bonded), each two of them form the mutually opposite grooves for one layer of strips. It is favourable if the frames have two clearances. The respectively smaller clearance of the frames is used in this case to form a shaft which is open at the top and bottom and into which a bag with drying agent can be placed. This bag may be stopped from falling out, for example by a paper wrapper.

The width of the grooves, and consequently the spacing between the layers of strips, is slightly more imprecise in this embodiment, since the joining tolerances have an effect.

As already mentioned at the beginning, it is required for the removal of test elements that the magazine has openings. It has proven to be advantageous if one or more openings are integrated in a side wall of the magazine. Such an opening is at the level of a groove, so that a test element which is in the groove alongside the opening can be removed from a magazine by displacement along its longitudinal axis. For this purpose, the opening preferably has a rectangular cross section, the height of which is 10 to 50% greater than the maximum height of the test elements and the width of which is 10 to 50% greater than the width of the test elements. If a plurality of pairs of grooves are used in one magazine, each pair of grooves preferably has a removal opening of this type. Furthermore, it is advantageous if each of the pairs of grooves has in the opposite side wall a further opening, through which a slide can penetrate into the magazine to push a test element out. The openings mentioned above may be at least partially closed by sealing films in a magazine brought onto the market. The sealing films can be pulled off before use. It is advantageous, however, if the sealing films are perforated by the slide or an emerging test element.

In a further, particularly simple embodiment of the magazine, the removal of test elements takes place by displacing the test elements beyond the end of the grooves (in the longitudinal direction of the grooves), i.e. a displacement transversely with respect to the longitudinal axis of the test elements takes place. In this embodiment, the grooves of a pair

of grooves are open on one side, so that pushing out of test elements over the end of the grooves is possible. The magazine thus has one end face which runs transversely with respect to the side walls of the magazine and in which there is for each pair of grooves an opening for the outlet of test elements. These outlet openings preferably have a rectangular cross section, the width of which is 10 to 30% greater than the maximum height of the test elements and the length of which is 0.5 to 20% greater than the length of the test strips. In a variant of this embodiment that is particularly simple to produce, the magazine has no end wall and, for transporting the magazine, the end face is closed merely by a sealing film. The sealing film may serve the purpose of closing the end wall against the ingress of moisture. If the moisture protection is realized in another way (for example by an outer packaging), however, it may be possible to dispense with the sealing film. However, it has been found to be particularly effective to stick a film over the end face in which the ends of the grooves are located. On the one hand, this stops the test elements from falling out, on the other hand the film can be perforated by the test elements. One particular advantage of this embodiment is that the film is opened only in the region of the layer from which removal takes place. The other (still complete) layers of test elements continue to be protected by the film, so that no test elements can fall out when a magazine is tilted.

For the successive removal of test elements from a magazine it is required that the test elements can either be transported into a removal position or are ejected directly out of the magazine. In the simplest case, for this purpose the magazine is arranged in such a way that the grooves are vertical and the test elements are transported downwards in the grooves by gravity. At the lower end of the magazine there is in this case a removal position, or the magazine is open, so that the test elements can emerge directly from the magazine. In the latter case, it is required that there is a closure which prevents uncontrolled falling out of test elements and makes successive removal possible.

The magazine preferably contains in its interior one or more spring elements, which transports the group of test elements located in a pair of grooves together in the direction of a removal position. Spring elements of this type may be, for example, spiral springs which are arranged at the end of each groove remote from the removal position. Spring elements also stabilize the arrangement of the test elements, even when the magazine is not completely filled. This avoids the test elements becoming skewed or disorderly in some other way, which would greatly reduce the reliability of a magazine.

In a particularly preferred embodiment of the magazine, it has in the upper side or underside at least one clearance, through which a slide can be introduced into the magazine. With such a slide, it is possible to perform the transporting of the test elements from outside. The slide may be fastened on the outer side of the magazine, so that it can be displaced manually by the user. However, the slide preferably belongs to an analysing device which works with test elements. The slide is in this case controlled by a drive unit belonging

to the analysing device, so that the removal of test elements by the analysing device can be controlled. This can achieve the effect that test elements are removed from the protective magazine only when they are needed by the analysing device.

A unit, comprising a magazine and a slide which serves for the removal of test elements, forms a system for making test elements available, which is likewise the subject-matter of this invention. Belonging to the system is a magazine with at least two opposite guide grooves, into which the test elements are pushed in such a way that they lie directly next to one another in a surface area, and the edges of neighbouring test elements butt against one another. Also belonging to the system is a slide, which acts on one end of the surface area formed by the test elements and displaces the test elements transversely with respect to their longitudinal axis in the direction of the opposite end of the surface area. As already described above, the said slide preferably engages in the magazine through a clearance in a wall of the magazine. The clearance needed for this purpose is kept as small as possible, to minimize any ingress of moisture into the magazine. The clearance is preferably a slit which runs parallel to the grooves in the upper side or underside of the magazine. The slit may have on the opposite longitudinal sides rubber lips which, in the position of rest, bear against one another and thus prevent to the greatest extent any ingress of moisture. For removal, a slide is introduced between the rubber lips and displaced along the slit. On account of the elastic property of the rubber lips, relatively small locations of permeability occur only in the region where a slide passes through, and the greatest part of the slit is adequately closed against moisture.

For the removal of test elements, the slide is displaced incrementally by a distance which corresponds essentially to the width of a test element, so that the test elements are successively brought into a removal position or else are ejected directly out of the magazine. The drive unit for the slide may be, for example, a nut which is located on a threaded rod. The threaded rod may be turned by a stepping motor, which for its part is activated by a control unit. As already mentioned above, it is advantageous if the control unit is connected to the control unit of the analysing device, so that the time of removal can be suitably controlled. The slide, for example in the form of a metal pin, may be fastened directly to the said nut. A rotation of the threaded rod brings about a linear advancement of the pin, which is used for the displacement of the test elements.

If a magazine with a plurality of pairs of grooves is used, it is advantageous if the depth of penetration of the slide into the magazine can be controlled. In an advantageous procedure, the slide initially penetrates into the magazine to such a depth that it is at the level of a first layer (level) of test elements, and transports the group of test elements located at this level, so that the individual test elements successively reach a removal position. After complete emptying of this layer, the slide travels back, the depth of penetration is increased, so that it is at the level of a second layer of test elements, and the removal operation is

repeated. Further layers of test elements can be emptied in a corresponding way.

For the successive removal of test elements from a magazine, it is important that the displacement of the test elements into the removal position within the magazine and the removal of the test elements from this position take place in a way coordinated with one another. The removal of test elements from the removal position may take place by a second slide, which displaces the test element respectively located in the removal position along its longitudinal axis and consequently pushes it out of the magazine. Furthermore, the removal may take place by a gripper being introduced into the magazine and pulling a test element out of the removal position. Combinations of the two removal operations, in which the test element is initially displaced a certain distance along its longitudinal axis by a slide, so that the test element can be gripped better by a handling unit, are also possible.

A removal cycle for test elements comprises the following steps:

- removal of a test element from a removal position of the magazine (may take place by pushing out, pulling out or a combination of the two operations)
- displacement of the group of test elements located on one level, so that a new group is transported into the removal position.

1 The present invention is explained in more detail on the basis of the following figures:

1 Figure 1A shows a test element in plan view;

1 Figure 1B shows a side view of a test element;

1 Figure 2 shows a section through a magazine along one level of test elements;

1 Figure 3 shows a section through a magazine along line of intersection A' in Figure 2;

1 Figure 4 shows a section through a magazine along the line B' in Figure 2;

1 Figure 5 shows an enlargement of a detail of the region X in Figure 4;

1 Figure 6 shows the prior art (US-3,918,910);

1 Figure 7 shows a magazine constructed from fitted-together frames.

1 Figure 1 shows a test element in plan view. The carrier 2 and the test zones 3 can also be seen. In Figure 1B, a further test element is represented in side view. Figure 1B shows in particular the different height of the test zones 3 and the bending of the carrier 2.

1 In Figure 2, a magazine is represented along one layer (level) of test elements 1. In a magazine, the test elements are arranged in the same sense side-by-side. In the side walls 10a and 10b are the grooves for receiving the test elements. On its rear side, the magazine has a drying-agent chamber 11, which serves the purpose of absorbing moisture which has penetrated into the magazine. Substances known from the prior art, for example silica gels or molecular sieves, are used as the drying agent. The drying-agent chamber 11 closes the rear side of the magazine in such a way that no openings remain, to prevent any ingress of moisture.

An already half-emptied layer of test elements is represented in Figure 2. For emptying, the test elements are moved from the rear side of the magazine in the direction of the front side 12, as is indicated by the arrow 13. The test element 1' closest to the front side is in the removal position. For removal, the test element 1' is pushed out of the magazine by a pushing-out slide 14 in the direction represented by the arrow 15. For this purpose, the magazine has in the right-hand side face 10b an opening through which the pushing-out slide 14 can penetrate into the magazine. Furthermore, a magazine has in the left-hand side face 10a an opening through which the test element 1' can emerge from the magazine.

Also represented in Figure 2 are the slits 16a and 16b, although they are located in the upper side of the magazine and do not lie on the level of the test elements. Slides which move the group of test elements in the direction of the arrow 13 can engage through the slits 16a and 16b.

Figure 3 shows a section through the magazine of Figure 2 along line A-A'. In Figure 3, the slide 17 for advancing the test elements in the direction of the removal position is represented. Furthermore, Figure 3 reveals the length L of the grooves.

Figure 4 shows a representation of the magazine from Figure 2 along the line of intersection B-B'. Figure 4 reveals the pairs of grooves 18a, 18b, in which the test elements are guided. Belonging to a pair of grooves there are respectively two opposite grooves. The magazine represented in Figure 4 has 12 such pairs of grooves, so that test elements can be stored on or in 12 levels or layers.

Figure 5 shows an enlargement (5 times) of a detail of the region X in Figure 4, in which the structure of the grooves used here can be seen more precisely. The grooves represented have a depth T to which the ends of the test elements are introduced. It can be seen from Figure 5 that each of the grooves has a narrower part and a wider part. This is advantageous if the test zones on the carrier reach close up to one end of the test element. In this case, a groove with two thickness regions can be advantageously used, so that the outermost end of a test element, which is not covered by a test zone, is guided through the narrower region of the grooves, and a neighbouring region, in which there is a test zone, can continue to be guided by the wider region of the groove.

The spacing of the grooves represented in Figure 5 is about 2 mm. Such a small spacing can be realized in spite of a bending of the test elements, without the risk of neighbouring levels of test elements catching. For this purpose, it is advantageous to arrange the test elements on the levels in the same sense, so that the upper side of a test element in one layer comes to lie alongside the underside of a test element in the next-higher layer. Since a bending of test elements normally occurs in the same direction for each batch, the layers of the test elements have the same direction of curvature and an adequate distance between the layers is preserved.

Figure 7 shows an exploded drawing of a magazine which is fitted together or

clipped together from individual frames 20. In the example represented, the frames are made in such a way that the lateral edge 21 is elevated with respect to a ledge 22. The underside of the frames in the region of the edge 21 and the ledge 22 is essentially planar, so that when two or more frames are stacked one on top of the other a groove formed by the ledge 22 and the bottom surface of the next frame lying over the said ledge is obtained. The frames have a front part, in which the grooves are located, and a rectangular clearance 23. In the fitted-together magazine, this leads to a hollow space which can be filled with a drying agent or a drying-agent container. The frames 20 may also have slits 24 (two in the example represented), into which a slide for displacing the test elements can engage.

1List of reference numerals

1	
11	test element
12	carrier
13	test zone
110a	left-hand side face
110b	right-hand side face
111	drying-agent chamber
112	front side
113	arrow in the direction of advancement
114	pushing-out slide
115	arrow in pushing-out direction
116a, 16b	slits
117	slide
118a, 18b	pair of grooves
120	individual frame
121	edge
122	ledge
123	rectangular clearance
124	slit

1Patent claims

1

11. Magazine for storing test elements with one or more test zones which are attached next to one another on a rectangular carrier, the magazine having at least one pair of opposite guide grooves, into which the test elements are pushed in such a way that they lie directly next to one another and edges of neighbouring carriers butt against one another.

12. Magazine according to Claim 1. with two or more pairs of opposite guide grooves, the pairs being arranged one above the other.

13. Magazine according to Claim 1 or 2. which has walls which close off the magazine with respect to the space outside.

14. Magazine according to Claim 2. in which the guide grooves are integrated into a side wall of the magazine and which has for each pair of guide grooves an opening which is arranged in a side wall.

15. Magazine according to Claim 4. in which the opening has a rectangular cross section, the height of which is 10 to 50% greater than the maximum height of the test elements and the width of which is 10 to 50% greater than the width of the test elements.

16. Magazine according to Claim 4. in which the magazine has an end face which runs essentially perpendicularly with respect to the side walls.

17. Magazine according to Claim 6. in which either there is in the end face an opening for each pair of grooves, which is arranged in such a way that test elements which are displaced in the grooves can emerge from the magazine through the opening, or the end face is open.

18. Magazine according to Claim 7. in which the opening has a rectangular cross section, the width of which is 10 to 50% greater than the maximum height of the test elements and the length of which is 0.5 to 20% greater than the length of the test strips.

19. Magazine according to Claim 3. comprising at least one clearance in a wall which runs parallel to the level of test elements.

110. Magazine according to 7. comprising spring elements which displace the test elements within the groove in such a way that a test element comes to lie opposite the opening and can be removed through the opening.

111. Magazine according to Claim 1. which contains a drying agent in its interior.

112. Magazine according to Claim 1. in which the front side of the magazine is at least partially closed by a sealing film.

113. Magazine according to Claim 1. in which the front side is at least partially closed by a sealing film and the rear side is closed by a drying-agent chamber.

114. Magazine according to Claim 1 or 13. which is constructed from the following elements:

- two side walls with integrated guide grooves,
- two walls which connect the side walls to one another in such a way that a cuboid is produced
- a drying-agent chamber which is arranged on the rear side of the magazine.

115. Magazine according to Claim 14, in which the open end face of the cuboid is at least partially closed by a sealing film.

116. Magazine according to Claim 14, in which the said parts are produced as contiguous injection-moulded parts and are connected to one another via film hinges.

117. System for making test elements available, comprising

- a magazine with at least two opposite guide grooves, into which test elements have been pushed in such a way that they lie directly next to one another in a surface area and edges of neighbouring test elements butt against one another,
- a slide, which acts against one end of the layer formed by the test elements and displaces the test elements along the grooves in the direction of the opposite end of the layer.

18. System according to Claim 17, in which the magazine has a wall with at least one clearance, through which the slide is introduced into the magazine.

19. System according to Claim 17, in which the slide is driven by a drive unit.

20. System according to Claim 19, in which the drive unit displaces the slide in a spatial direction incrementally by a distance which corresponds essentially to the width of a test element.

21. System according to Claim 19 or 20, in which the drive unit controls the depth of penetration of the slide into the magazine.

22. System according to Claim 17, with a second slide, which transports a test element located in a removal position out of the magazine by displacement along in the longitudinal direction of the test element.

23. System according to Claim 22, in which the magazine in the removal position has a first opening and a second opening and the second slide penetrates into the first opening and pushes the test element located in the removal position out through the second opening.

5 associated pages of drawings

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Fig. 3

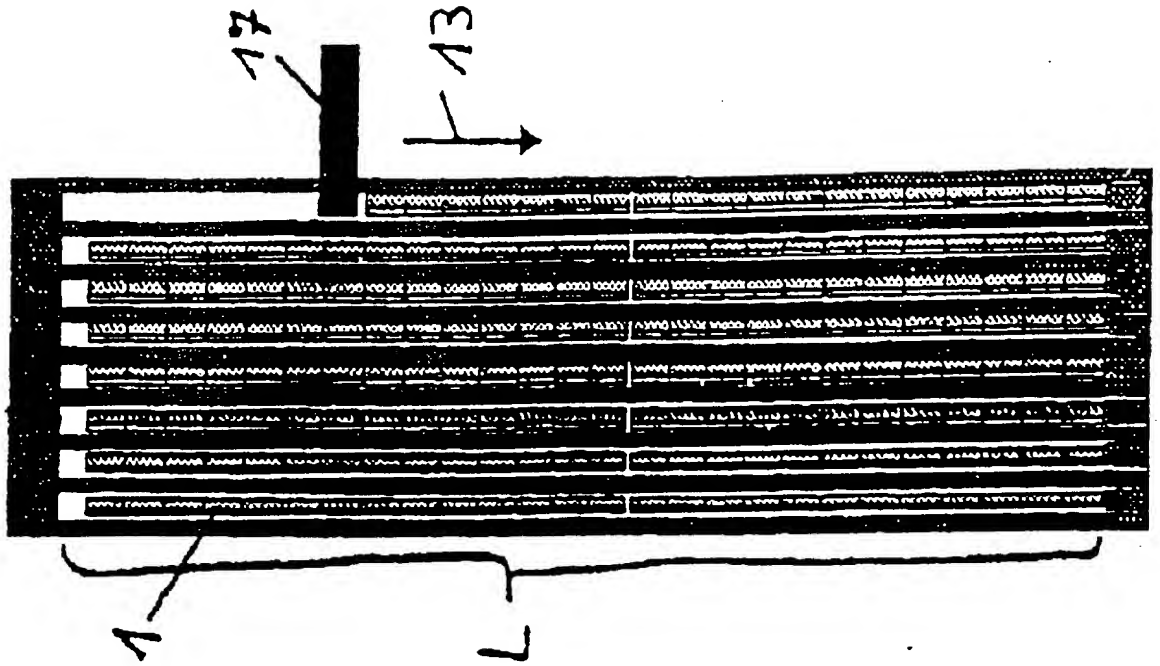

Fig. 2

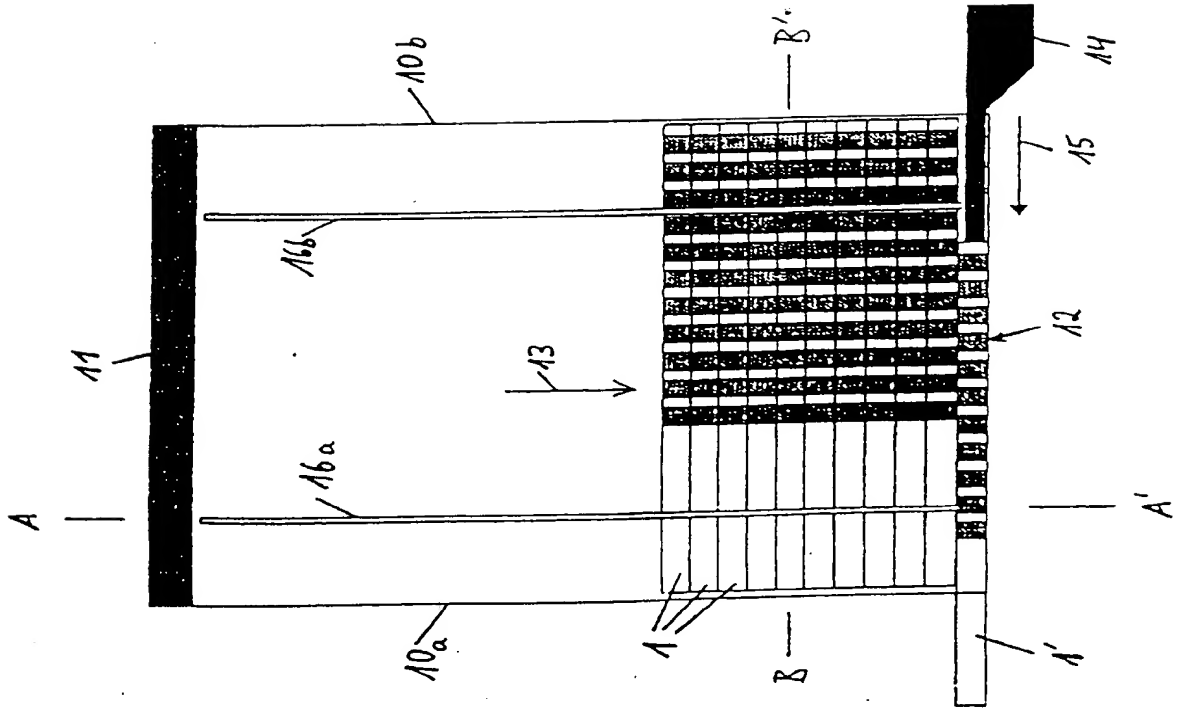

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Fig. 4

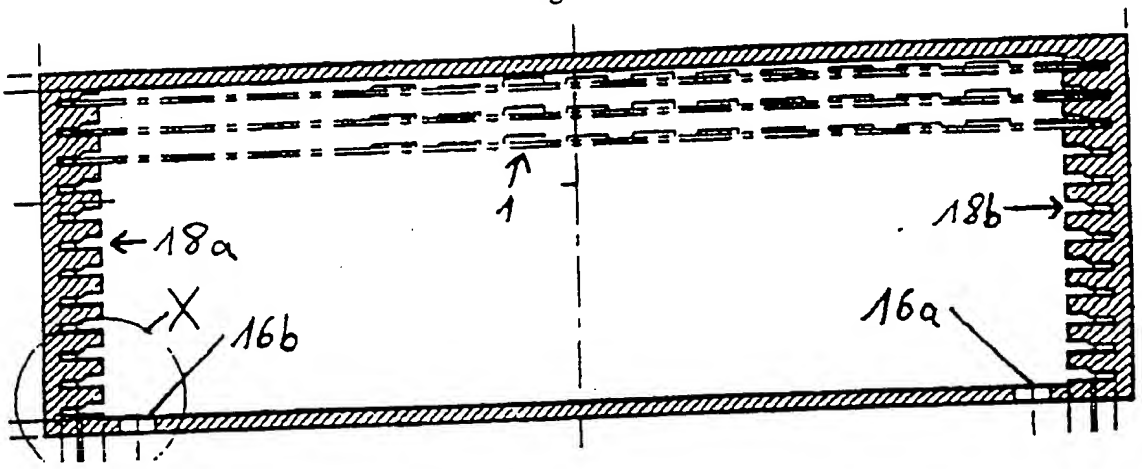

Fig. 5

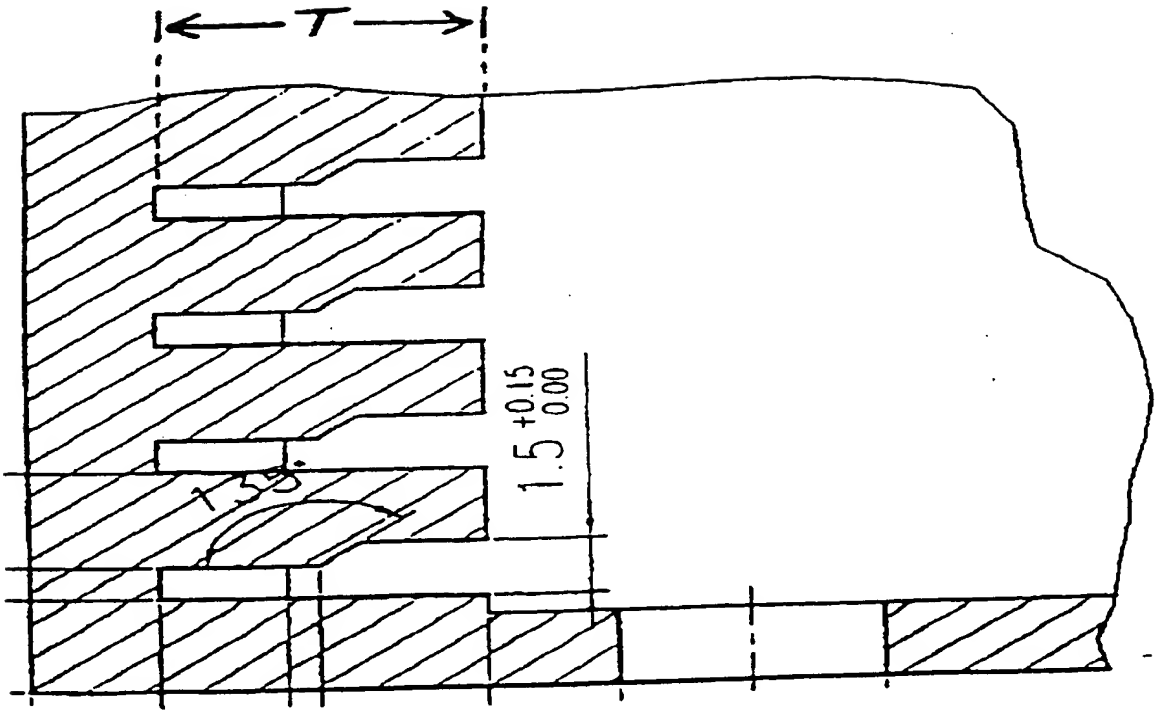

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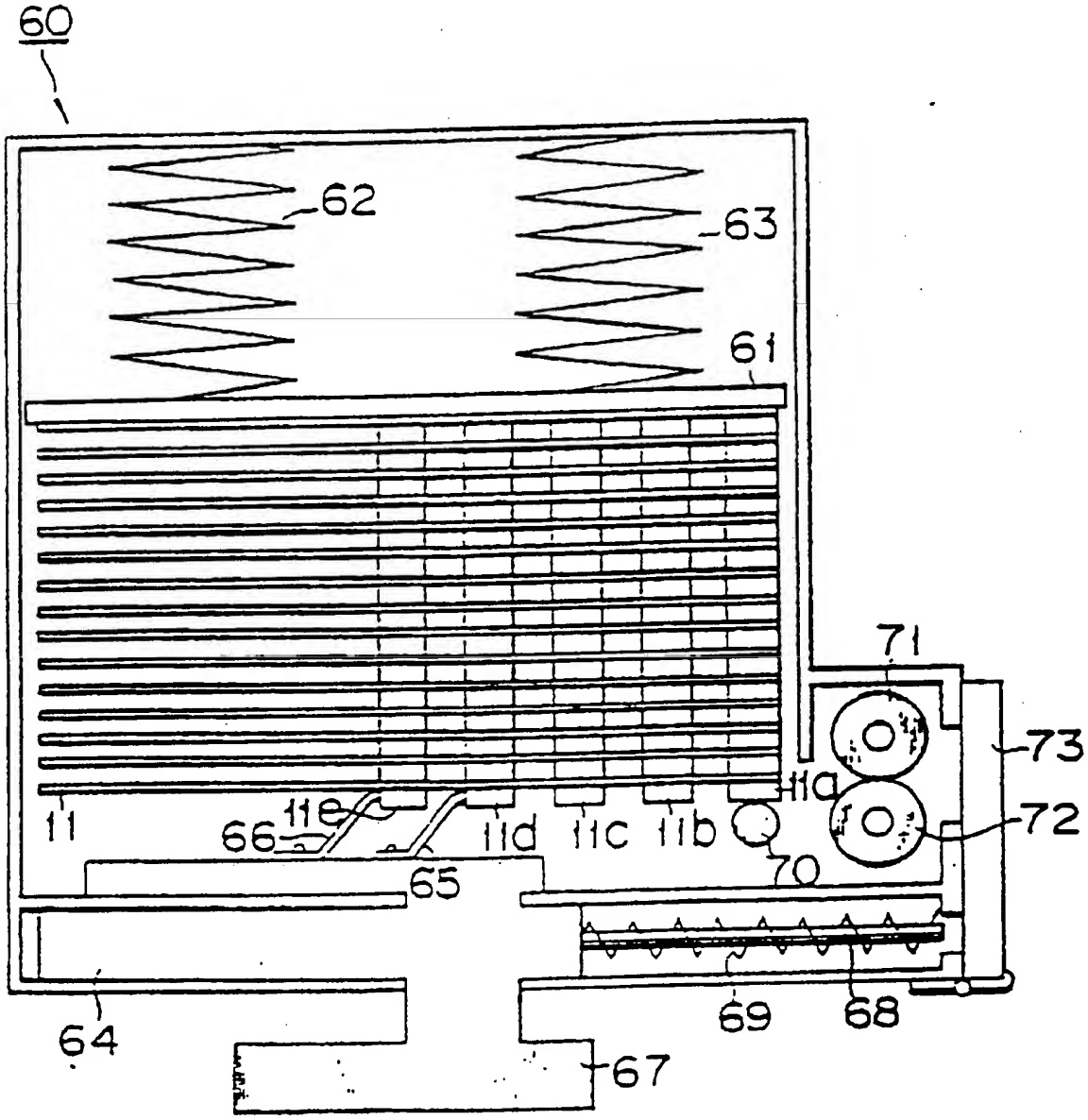
Fig. 6



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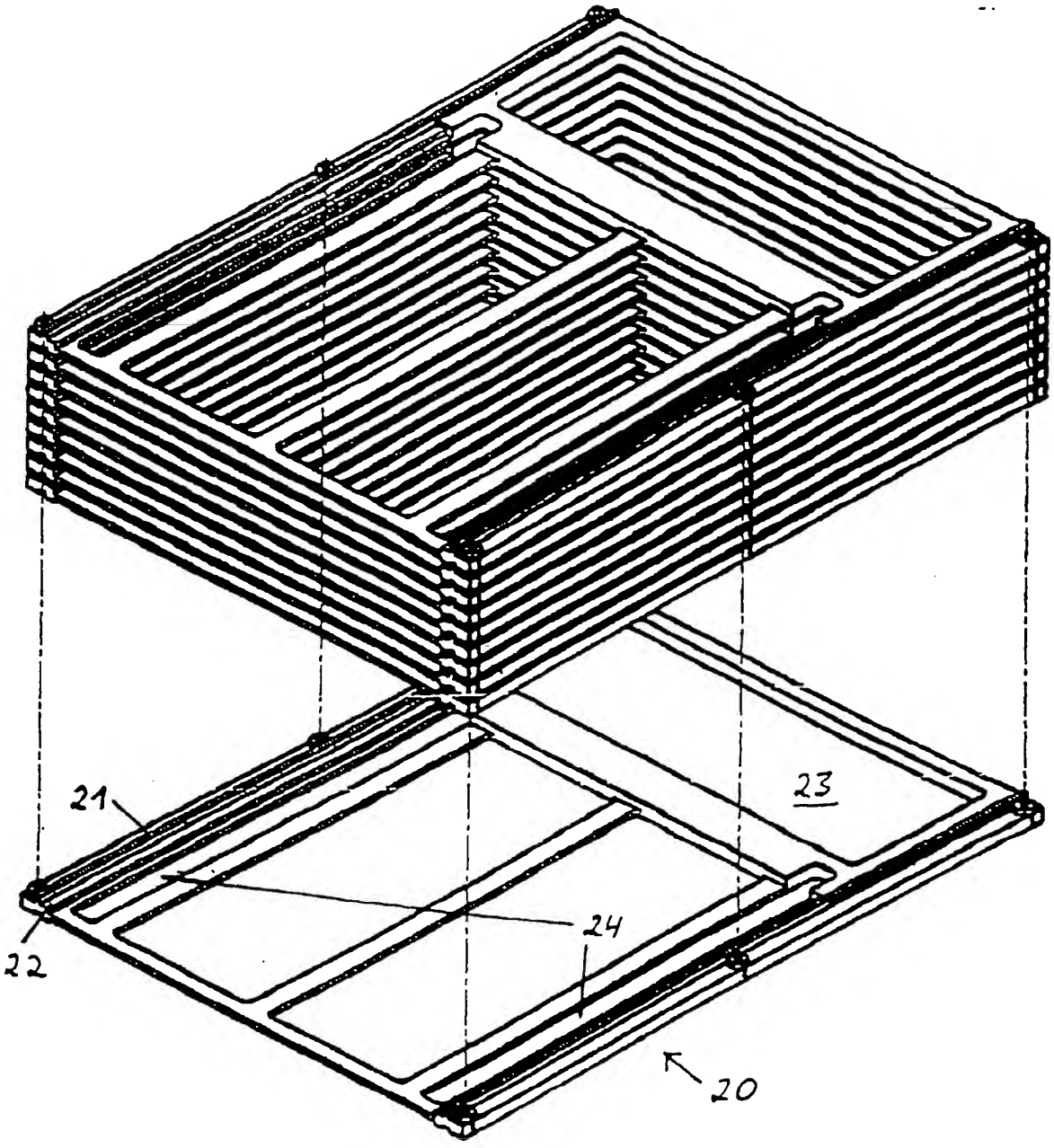
Laid open: 15 October 1998

Fig. 7



DRAWINGS PAGE 1

Number: DE 197 15 031 A 1
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Fig. 1A

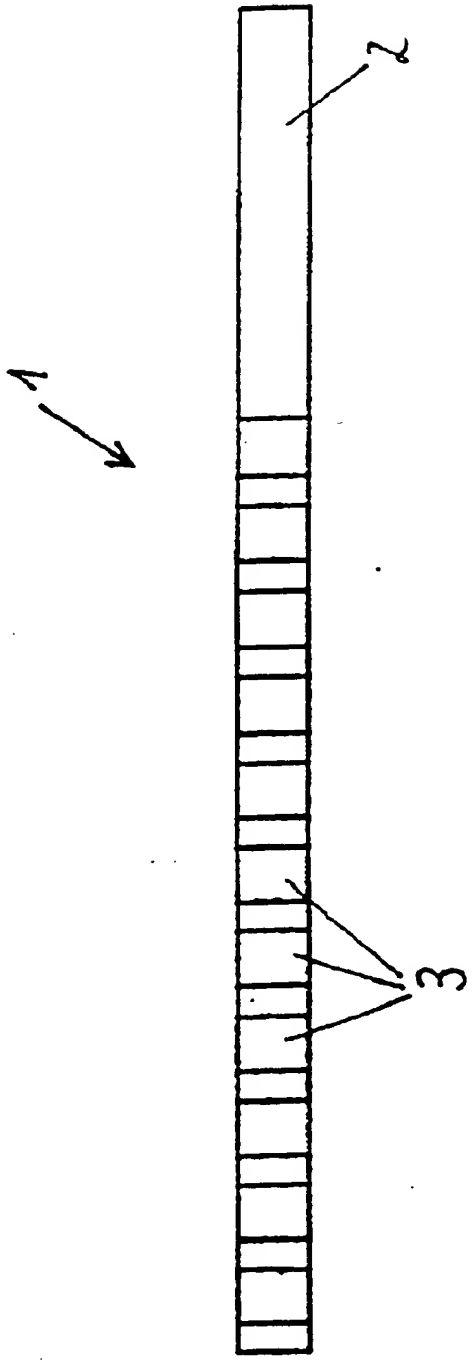

Fig. 1B